REMARKS

Upon entry of this paper, claims 34, 91-94, 98, 100, and 117-129 will be pending and under consideration. Claim 34 has been amended to specify an antibody to a human Notch protein, or a fragment of said antibody containing the idiotype thereof, which antibody or fragment inhibits binding of the human Notch protein to a Delta protein or to a Serrate protein. Support for this amendment is found in the specification at page 5, lines 1-7; page 11, lines 15-22; page 13, lines 20-23; p. 56, lines 5-7, and page 57, lines 7-8.

New claims 117-129 have been added. The new claims are supported in the specification at page 56, line 10-11, 15-16; and page 57, lines 7-8, 18-20. Claims 96-97, 99, and 101-116 have been canceled without prejudice, of which claims 101-106, 108-111, 113-114, and 116 were withdrawn as drawn to a non-elected species. Applicants reserve the right to prosecute the subject matter of the canceled claims in related application(s).

No new matter has been added by the amendments to the claims.

I. THE WRITTEN DESCRIPTION REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 34, 91-94, and 100 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner alleges that "the claimed therapeutic method still encompasses the treatment of a broad spectrum of diseases and disorders comprising the use of a genus of protein, antibody and oligonucleotide molecules defined functionally but not structurally" (Office Action, p. 4). The Examiner alleges that in view of the specification's definition of "toporythmic genes," the claims "encompass any gene or gene product *yet to be identified* as interacting with any of Notch, Delta, or Serrate" (Office Action, p. 5). The Examiner adds that "the protein that inhibits Notch interactions is not limited to antibody molecules as Applicant implies[1], but encompasses...also protein molecules which indirectly antagonize Notch function..." (Office Action, p. 6). Applicants respectfully disagree with the Examiner's rejection, and submit that the present specification provides a sufficient written description of the claimed invention as amended herein.

Firstly, Applicants point out that claim 34, upon which claims 91-94 and 100 depend, has been amended to recite an antibody to a human Notch protein, or fragment of said antibody containing the idiotype thereof, which antibody or fragment inhibits binding of the human Notch

[1] Applicants disagree that this was implied by Applicants in their prior-filed papers.

protein to a Delta protein or to a Serrate protein. Thus, in view of this amendment, the antibody specified by the claims is an antibody to a human Notch protein, that directly inhibits the binding of the human Notch protein to its ligand, which is a Delta or a Serrate protein.[2] Therefore, the aspect of the Examiner's rejections based on the recitation of toporythmic proteins/genes in the claims is obviated.

In order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). This inquiry is often phrased as whether the patent specification provides "adequate support" for the claim(s) at issue. *Id.* at 1560. The description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the claimed genus. *Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). Moreover, in *Centocor Ortho Biotech, Inc., v. Abbott Labs.*, 636 F.3d 1341, 1352 (Fed. Cir. 2011), the Federal Circuit addressed the issue of what constitutes adequate written description in claiming antibodies, to a well-characterized antigen, with specific properties. There, the court found a lack of written description where obtaining the antibody in question was not possible, as of the priority date, with the use of "'conventional,' 'routine,' 'well developed and mature' technology." *See id.* The court held that the patent holder failed to support its contention that generating "antibodies with the claimed properties would be straightforward for a person of ordinary skill in the art" given the state of the art as of the priority date. *See id.* In doing so, the court emphasized that "the written description does not demand either examples or an actual reduction to practice." *Id.*

With respect to antibodies to human Notch protein, the Examiner alleges that

> the claims recite that the antibody must also be a molecule which antagonizes the function of Notch protein, such as a neutralizing antibody, consistent with the therapeutic intent of the method. No such neutralizing antibodies are demonstrated by the instant specification, nor would the skilled artisan be able to readily distinguish such neutralizing antibodies from the genus of anti-Notch antibodies encompassed by the claims

(Office Action, p. 7).

[2] The term "Serrate protein" is intended to include mammalian Serrate proteins, such as Jagged.

The Examiner acknowledges that antibodies that specifically bind to human Notch protein or antibodies containing the idiotype thereof meet the written description requirement (Office Action, p. 7). The Examiner alleges, however, that "neutralizing antibodies are not demonstrated by the instant specification nor would a skilled artisan be able to readily distinguish such neutralizing antibodies from the genus of anti-Notch antibodies encompassed by the claims" (Office Action, p. 7). For the following reasons, Applicants respectfully disagree.

The antibodies specified in the claims as amended are antibodies to human Notch that the property of inhibiting binding between the human Notch protein and a Delta or Serrate protein (Delta or Serrate proteins being known Notch ligands). Pursuant to the guidance of *Centocor*, discussed above, the specification provides an adequate written description for such a particular class of antibodies if the antigen is well-characterized and an antibody with the recited property can be obtained using conventional, routine technology, *i.e.*, it would be straightforward for one of skill in the art to generate antibodies with such property. These criteria for an adequate written description are clearly satisfied in the instant case.

Firstly, human Notch proteins are well-characterized by the instant specification. The instant specification discloses the amino acid sequences of two human Notch proteins, with structural domains indicated (*see* p. 10, lines 7-14 and Fig. 13).

Secondly, routine, conventional, mature technology can be used in a straightforward manner to obtain an antibody that has the property of inhibiting binding between Notch and one of its ligands, Delta or Serrate. Methods for identifying inhibitors of binding between a cell surface receptor and its ligand are well known in the art, *e.g.*, ELISAs (*see* specification at p. 57, lines 14-20). Furthermore, the specification describes in detail an assay that can be used, and actually was used, for detecting binding, and inhibition thereof, between Notch and its ligand. Section 6 of the specification describes an assay that was used to detect Notch-Delta binding, by recombinantly expressing the Notch and Delta genes in *Drosophila* Schneider's 2 (S2) cells and scoring the cells for their ability to aggregate (*see* specification at pp. 57-67; this assay is also taught in Fehon *et al.*, 1990, Cell, 61:523-534 (Ref. C22, of record)).

Section 7 of the specification (pp. 67-75) discloses the use of such an aggregation assay using different deletion mutants of Notch to determine that EGF-like repeats 11 and 12 are necessary and sufficient for binding between Notch and Delta. Section 8 of the specification (pp. 75-77) employs this very same S2 cell aggregation assay to detect binding between Notch and Serrate.

Moreover, Section 6.2.2 expressly teaches using such an assay to determine whether antibodies to Notch inhibit binding between Notch and Delta. Antisera to Notch extracellular domain fusion proteins were found to inhibit Notch-Delta binding and thus the aggregation of cells in the assay. Indeed, the ability of such antisera to inhibit Notch-Delta binding predicts that antibodies to human Notch that inhibit such binding can routinely be identified. Thus, the specification provides an assay that can be routinely employed in a straightforward manner to determine whether an antibody to a human Notch protein inhibits binding of a human Notch protein to a Delta or Serrate protein.

The Examiner further contends that, while the prior art references teach the sequences of members of the Notch group of genes, "they are silent with respect to which portions of the encoded proteins are necessary or sufficient for Notch interaction" (Office Action, p. 6). Applicants submit that the specification teaches the amino acid sequences within human Notch that are necessary and sufficient for protein-protein interactions, *i.e.*, ELR-11 and ELR-12 (the binding region of Notch responsible for binding to Delta and Serrate) (*see* the specification at Sections 7-8 on pp. 67-77; Fig. 4).

Therefore, there is an adequate written description for the use of a genus of anti-human Notch antibodies which inhibits binding between a human Notch protein and a Delta or Serrate protein, as claimed.

In view of the foregoing, Applicants respectfully request withdrawal of this Section 112, first paragraph, rejection.

II. THE ENABLEMENT REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 34, 91-94, and 100 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, the specification does not reasonably provide enablement for a method of treating "Notch- or Notch derivative-associated malignancy comprising the use of a genus of protein, antibody or oligonucleotide molecules" (*see* Office Action, p. 11). Applicants respectfully disagree with the Examiner and submit that the full scope of the presently pending claims, as amended herein, can be practiced by one skilled in the art without undue experimentation, and thus, the presently pending claims meet all the requirements set forth under 35 U.S.C. § 112, first paragraph.

As discussed above, claim 34, upon which claims 91-94 and 100 depend, has been amended to recite the administration of an antibody which inhibits binding of a human Notch

protein to a Delta protein or to a Serrate protein. Therefore, the aspect of the Examiner's rejection of the claims based on the recitation of toporythmic proteins/genes or Notch antisense oligonucleotides is obviated.

Applicants respectfully disagree with the Examiner's rejection with regards to the claims as amended, and submit that the specification clearly enables one of skill in the art to practice the full scope of the claimed methods, as amended herein, without undue experimentation. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *See Fields v. Conover*, 443 F.2d 1386, 1391, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. *See id.* The test for undue experimentation is not merely quantitative, "since a considerable amount of experimentation is permissible, if it is merely routine", *i.e.*, "[t]he key word is 'undue,' not 'experimentation'". *See id.*

Preliminarily, the Examiner alleges that the "malignancy to be treated in the claims need only express a Notch derivative that is related to a known Notch receptor only in that it can be bound by an antibody that binds a Notch protein, which allows for great breadth considering the varying affinities of antibodies and possible amount of cross-reactivity a given antibody could have" (Office Action, p. 11). Applicants respectfully disagree that the foregoing is a valid basis for the rejection for lack of enablement.

The Examiner's attention is respectfully directed to the data in Section 10.1 of the specification at pages 85-87. As clearly disclosed therein, the increased expression of human Notch protein in human tumors was identified through the quantitation of the amount of binding by the tumor tissue of an anti-human Notch antibody. That is, the tumors were actually determined to have increased expression of a molecule with Notch antigenicity, *i.e.*, a Notch protein or a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said expression in non-malignant samples. The "malignancy" recited in the instant claims is similarly defined in part as being characterized by increased expression of a human Notch protein or of a Notch derivative capable of being bound by an antibody to a human Notch protein, relative to said Notch activity or expression in an analogous non-malignant sample. Thus, the breadth of malignancies specified in the claims, referred to by the Examiner, is

consistent with the data in the specification. The Examiner has come forward with no reasonable basis to doubt the enablement. Thus, the rejection should be withdrawn.

Applicants submit that the specification provides considerable guidance and direction to practice the claimed invention without undue experimentation, and incorporate by reference their remarks made in the Reply dated February 11, 2008, in the Reply dated November 14, 2008, and in the Reply dated December 21, 2009, submitting that one skilled in the art would not have to engage in undue experimentation in order to practice the claimed invention, and present additional remarks below.

As discussed above, the specification presents data showing that antisera to Notch extracellular domain fusion proteins inhibited binding between Notch and Delta. The ability of such antisera to inhibit Notch-Delta binding predicts that antibodies to human Notch that inhibit such binding can routinely be identified.

Additionally, the Examiner's attention is respectfully directed to the following post-filing date references[3], which demonstrate that antibodies to human Notch protein that inhibit binding between Notch and Delta or between Notch and Serrate can be obtained and that such antibodies are indicated for use in the treatment of malignancy.

Aste-Amézaga *et al.*, 2010, PLoS One, 5:e9094 describes anti-Notch1 antibodies directed towards the EGF-like repeats region (1-13), encompassing the ligand-binding domain ("LBD"). Aste-Amézaga *et al.* demonstrates that most of the selected, high affinity antibodies to the Notch1 extracellular domain inhibited binding between the Notch1 ectodomain and a Delta protein (DLL4) (Aste-Amézaga *et al.*, paragraph spanning pp. 4-5). The antibodies that did not inhibit such binding recognized the NRR domain rather than the EGF-like repeat domain (the LBD) (Aste-Amézaga *et al.*, paragraph spanning pp. 4-5). Anti-Notch1 antibodies directed towards the LBD were able to completely inhibit Notch1 activation by Jag2, a human homolog to Serrate (Aste-Amézaga *et al.*, p. 5, 2nd col.). Moreover, LBD antibodies also were able to inhibit Jag1-, Jag2-, and DLL1 (Delta-like1; a human homolog to *Drosophila* Delta)-dependent Notch signaling (Aste-Amézaga *et al.*, p. 6, 1st col.; Table 2). Furthermore, the LBD antibodies did not exhibit agonistic activity (Aste-Amézaga *et al.*, p. 5, 2nd col.). Aste-Amézaga *et al.* also states that the inhibitors of the Notch signaling pathway "represent an opportunity for targeted treatment of several different human cancers" and specifically references breast cancer as one such malignancy (Aste-Amézaga *et al.*, p. 9, 2nd col.). Furthermore, Aste-Amézaga *et al.* notes

[3] Applicants note that post filing date references can be used to show the accuracy of a statement made in the specification. See *Application of Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A., 1971), fn. 4.

that "[t]he antibodies recognize endogenous receptors on tumor cell lines, inhibit the expression of Notch target genes in some tumor cell lines, and block Notch-dependent transcription in transfected cells" (Astc-Amézaga *et al.*, p. 10, 1st-2nd col.).

The Examiner contends that Li *et al.*, 2008, J. Biol. Chem., 283:8046-8054 (Ref. C103, of record) demonstrates "that Notch-3 specific antibodies directed against the EGF repeat region (which would comprise ELR-11 and ELR-12) are either very weak or ineffective in inhibiting various types of ligand-induced Notch-3 signaling" (Office Action, p. 16). However, Applicants point out that Li *et al.* still demonstrates that antibodies specific for the EGF-repeat region of Notch3 inhibited Notch3 activation (which the reference states is "perhaps through competition for ligand binding") and that such antibodies were only described as weak antagonists of JAGGED1 (a mammalian Serrate)- and DLL4 (a Delta)-induced Notch3 signaling in contrast to the more potent inhibition of the antibodies to the NRR domain (*see* Li *et al.*, p. 8049, 2nd col.).

The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Federal Circuit explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "*unless* there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "*must* be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the Federal Circuit in *Brana* explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441. In the present invention, Applicants have provided such evidence showing, *inter alia*, that anti-Notch antibodies are capable of inhibiting binding between a human Notch protein and its ligand, a Delta or Serrate protein, that activated Notch function is associated with malignancy, and that antagonizing the function of a Notch protein should have anti-tumor therapeutic value.

The foregoing evidence is sufficient to convince one skilled in the art of Applicants' asserted utility, *i.e.*, that an antibody to a human Notch protein, or fragment of said antibody containing the idiotype of thereof, which antibody or fragment inhibits binding of the human Notch protein to a Delta protein or to a Serrate protein can be used to treat a malignancy. The claimed invention thus satisfies 35 U.S.C. § 112, first paragraph.

Thus, it is respectfully requested that this rejection of claims 34, 91-94 and 100 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

III. THE INDEFINITENESS REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 34 and 91-94 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner contends that the recitation of an oligonucleotide which "'consists of at least six nucleotides' is ambiguous and indefinite because it is unclear whether the oligonucleotide is limited to 6 nucleotides total or whether longer sequences are encompassed by the claim" (Office Action, p. 27). Similarly, the Examiner alleges that the phrase, "'consists of at least a sequence complementary to at least a portion of a RNA transcript...' is ambiguous because it is unclear whether the oligonucleotide is limited to a specific sequence or whether it may contain other elements" (Office Action, p. 27-28). Applicants point out that claim 34, upon which claims 91-94 depend, has been amended and no longer recites "oligonucleotide" and the allegedly ambiguous language. Accordingly, Applicants believe the claim amendments obviate the rejection, and thus, respectfully request that the rejection be withdrawn.

IV. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION VIEW OF COPENDING APPLICATION NO. 11/546,583

Claims 34 and 91-94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 99, 106, and 107 of copending Application No. 11/546,583 ("the '583 Application"). The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass treatment of a subject having a disease or disorder that is a malignancy characterized by increased Notch activity or increased expression of a Notch protein comprising administering a protein which is able to antagonize Notch function" (Office Action at p. 29). Applicants traverse this rejection.

Applicants respectfully direct the Examiner's attention to MPEP § 804(I)(B), which provides:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier filed application to issue as a patent without a terminal disclaimer.

MPEP § 804(I)(B)(1).

Applicants respectfully submit that with the withdrawal of the rejections discussed above, the only remaining rejection in the instant application is the outstanding provisional obviousness-type double patenting rejection. Applicants further submit that for the purposes of this obviousness-type double patenting rejection, the instant patent application is the "earlier filed application," since it has the earliest effective filing date. *C.f. In re Fallaux,* 564 F.3d 1313 (Fed. Cir. 2009); *In re Braat,* 937 F.2d 589 (Fed. Cir. 1991). As such, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection and allowance of the pending claims.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history of the present application.

Applicants request that the Examiner call Adriane M. Antler at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

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Enclosures